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Effectiveness of preemptive intra-articular levobupivacaine on pain relief after arthroscopic knee surgery

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ABSTRACT

Background and Aim: Severe pain and comfortlessness may be seen in patients after arthroscopic knee surgery despite various commonly administered analgesic methods, particularly based on local anesthetics. The aim of this study was to determine the effect of intraarticular levobupivacaine injected preoperatively on pain relief and time to first analgesic request during the postoperative period.

Material and Methods: 40 adult-patients, ASA I and II, undergoing elective arthroscopic surgery were included in the study. Patients in the levobupivacaine group received intra-articular levobupivacaine at 5mg/ml dosages and 20 ml total volume 30 min before the procedure. Patients in the control group received 20 ml of normal saline. Visual analogue scale (VAS) scores were assessed at the 1st, 2nd, 4th, 8th, 12th and 24th hour postoperatively. Time to first analgesic request and total analgesics used over the course of 24 hours after the surgery were recorded. All patients received continuous morphine infusion via patient controlled analgesia (PCA) devices postoperatively. Additionally, patients' pain satisfaction scores were recorded.

Results: Lower VAS scores at the 1st, 2nd, 4th and 8th hours postoperatively - both at rest and during motion - were found in the levobupivacaine group compared to the normal saline group ($p<0.001$, $p<0.001$, $p<0.001$ and $p<0.02$ respectively). Time to first analgesic request was longer with the levobupivacaine group than the group with saline (22.50 vs 15.00 min, $p<0.02$). A significant difference was found in consumed total opioid doses (9.10 vs 31.75 mg, $p<0.001$). The number of analgesic demands using PCA were significantly different between groups (10.80 v.s. 36.1 times in 24 hours, $p<0.001$).

Conclusion: Preemptive analgesia using intraarticular levobupivacaine 5 mg/ml (20 ml total volume) provides better pain control - evaluated through VAS scoring, time to first analgesic request and opioid consumption - compared to saline in patients undergoing arthroscopic knee surgery.

Key words: Preemptive analgesia, arthroscopy, intra-articular injection, levobupivacaine

Introduction

Knee arthroscopy is a commonly performed surgical procedure and patients may suffer from severe pain and discomfort in its aftermath. This may lead to a delayed rehabilitation process and discharge from the hospital. Therefore, early aggressive pain treatment during the postoperative period is required.

Local anesthetics are commonly used in the treatment of pain following arthroscopic procedures [1]. Levobupivacaine is an S (-) isomer of racemic bupiv-

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acaine. Despite long-acting effects and similar properties to bupivacaine, Levobupivacaine is less toxic than bupivacaine [2]. Preemptive analgesia provides effective pain control subsequent to arthroscopic surgery and reduces postoperative opioid requirements [3]. However, there are limited studies in this field.

In the work presented here, we sought to investigate whether preemptive intra-articular levobupivacaine reduces postoperative pain levels, analgesic requirements and time to first analgesic request.

Material and Methods

This study was conducted by the Department of Anesthesiology and Reanimation at the Hacettepe University Faculty of Medicine between July 2009 and October 2009. A total of 40 adult patients, all being volunteers and american society of anesthesiologist (ASA) I or II undergoing elective arthroscopic surgery, were enrolled. Our study was performed in accordance with the current Declaration of Helsinki. It was approved by the research ethics committee of Hacettepe University (07.02.2009/LUT09/55-51) All patients were informed about the study and detailed written consent was obtained. Patients with severe systemic disease, allergies to the studied medication(s), taking long-term analgesic therapy, analgesics or non-steroid antiinflamatuar drug (NSAID) over the previous 24 hours, having had anterior cruciate ligament reconstruction, and having experienced traumatic injuries were excluded from the study.

The information on VAS was provided to all patients before the procedure (0: no pain, 10: the worst) and patients' pain scores were recorded both at rest and during knee movements. No patient was supplied with premedication. Electrocardiography (ECG), pulse oximetry and non-invasive blood pressure monitoring was performed on all patients in the operation room.

Patients were randomly divided into two groups. Randomization was performed by computer. In the first group (Group L), intra-articular levobupivacaine was injected at a 5mg/ml dosage and 20 ml total volume 30 min before the procedure while patients in the second group (group SF) were administered 20 ml of normal saline. None of the patients were treated with intra-articular drainage.

Anesthesia induction was performed in all patients with 3 mg / kg propofol and 1 μg / kg fentanyl. After induction, laryngeal mask airways were inserted to maintain ventilation. Following the end of surgery, the VAS scores were assessed both at rest and during knee movements at the 1^{st}, 2^{nd}, 3^{th}, 4^{th}, 8^{th}, 12^{th} and 24^{th} hours following surgery. Also, the time of first analgesic demand and the amount of total analgesics used over 24 hours after surgery were recorded. All patients received continuous morphine infusion via patient controlled analgesia (PCA) devices during the postoperative period (baseline = no, bolus = 1 mg, lockout = 10 min). Patients' satisfaction scores were recorded (0 = dissatisfied, 1 = somewhat satisfied, 2 = satisfied, 3 = very good, 4 = excellent).

Statistical Analysis

Statistical analysis was performed with SPSS 10,0 for Windows (SPSS Institute, Chicago, USA). In all analyses, $p < 0.05$ was considered significant. Data are presented as mean values and standard deviation (mean±SD). Demographic data, duration of anesthesia and surgery, time to first analgesic request and total analgesic consumption between the groups were analyzed through analysis of variance (ANOVA) followed by the Bonferroni method when significance was obtained. Pain scores and the number of analgesics consumed were evaluated with the Kruskal-Wallis test. Wilcoxon signed-rank test was used to compare postoperative VAS values to the preoperative VAS values. Patient satisfaction among groups was assessed using the χ^2 test. The number of patients requiring supplemental analgesics and the incidence of side effects were analyzed with Fisher's test and the χ^2 test.

Results

There were 8 female and 12 male patients in Group L and 6 male and 14 female patients in Group SF. While 8 patients underwent right knee surgery in Group L, 12 patients had a left knee operation. In Group SF, 8 patients underwent right knee surgery while 12 patients had left knee operations. There was no significant difference in demographic characteristics between the SF and L groups ($p > 0.05$) (Table 1).

The anesthesia and operation times is listed in table 2. There was no significant difference between groups in terms of anesthesia and surgery durations ($p > 0.05$).

In Groups L and SF, the first analgesic requirements

Table 1. Demographic characteristics (average ± SEM).

	GROUP L	GROUP SF	P Value
Age	44.65±14.43	48.20±14.87	0.4
Body Weight (kg)	77.95±11.69	75.75±10.47	0.5
Height (cm)	169.30±8.22	166.35±9.53	0.3

L: Levobupivacaine, SF: Normal Saline

Table 2. Anesthesia and operation time.

	GROUP L	GROUP SF	P Value
Anesthesia time	72.75±22.85	70.50±28.64	0.7
Operation time	46.00±19.44	50.75±24.40	0.7

L: Levobupivacaine, SF: Normal Saline

Table 3. Analgesic requirements and VAS values in both groups.

	GROUP L	GROUP SF	P Value
First Analgesic requirements (min.)	22.50(0;480)	15.00(3;30)	0.02
VAS at rest, postop 1hr. (cm)	5(0;8)	8(5;10)	0.00
VAS at rest, postop 2hrs. (cm)	4(0;6)	7.5(3;10)	0.00
VAS at rest, postop 4hrs. (cm)	2(0;5)	5(0;8)	0.00
VAS at rest, postop 8hrs. (cm)	0(0;4)	2.5(0;8)	0.02
VAS at rest, postop 12hrs. (cm)	0(0;1)	0(0;6)	0.39
VAS at rest, postop 24hrs. (cm)	0(0;0)	0(0;5)	0.79

L: Levobupivacaine, SF: Normal Saline

Table 4. VAS values in motion.

	GROUP L	GROUP SF	P Value
VAS, 1 hr.	6(0;9)	8.5(6;10)	0.00
VAS, 2 hrs.	4(0;7)	8(3;10)	0.00
VAS, 4 hrs.	2(0;6)	6.5(0;9)	0.00
VAS, 8 hrs.	0(0;4)	4(0;9)	0.003
VAS , 12 hrs.	0(0;2)	0(0;6)	0.25
VAS, 24 hrs.	0(0;0)	0(0;5)	0.79

L: Levobupivacaine, SF: Normal Saline

and VAS scores at the postoperative 1st, 2nd, 4th, 8th, 12th and 24th hours were compared (Table 3). In group L, the mean time to first analgesic request was 22:50 min (95% CI, 0 to 480) while it was and 15:00 min in Group SF (95% CI, 3 to 30), which was statistically significant ($p<0.02$). Compared to VAS at rest, there were statistically significant differences between groups at the 1st ($p<0.001$), 2nd ($p<0.001$), 4th ($p<0.001$) and 8th ($p<0.02$) hours. There was no statistically significant difference between VAS scores at the postoperative 12th and 24th hours ($p = 0.39$, $p = 0.79$). Similar results were demonstrated for VAS scores during motion (Table 4).

A significant difference was found for total consumed opioid doses between the two groups (9.10 v.s. 31.75 mg, $p<0.001$). The number of analgesic demands recorded by PCA devices were significantly different between groups (10.80 v.s. 36.1 times, $p<0.001$). The mean number of administered bolus doses was 9:15 times in Group L while it was 31.8 times in Group SF ($p<0.001$).

The median value for the degree of patient satisfaction in group L was 3 (2 and 3) and for the saline group, the median value was 2 (2 and 4) for saline group ($p<0.002$). None of the patients developed medical complications and/or suffered from side effects of the study drugs.

Discussion

In this study we observed lower VAS scores at the 1st, 2nd, 4th and 8th hours postoperatively, a longer time period required for first analgesic request, low doses of analgesics administered via PCA devices and higher patient satisfaction rates with preemptive levobupivacaine administered intra-articularly 30 minutes before surgical incision versus the control (normal saline administered at an equal volume). The relief of pain intensity and the reduction of pain-induced stress responses using analgesics before painful stimuli and reducing the need for postoperative analgesics is defined as preemptive analgesia [4]. The primary goal of preemptive analgesia is to prevent pain hypersensitivity resulting from two different surgical injury mechanisms. These mechanisms include peripheral sensitization, referring to peripheral nociceptor threshold reduction secondary to local noxious impulses and followed by central sensitization emerging from increased excitability of the dorsal horn neurons of the central nervous system secondary to increased input from peripheral afferent neurons [5]. In order to prevent activation of these mechanisms, preemptive analgesia is administered with a number of agents via different routes before surgical intervention and thus postoperative pain may

be diminished. In order to prevent a possible washout effect, varying time intervals between 15 and 30 min were used in several clinical studies investigating bupivacaine with or without adrenaline and/or morphine [1,6-9]. In only one study, conducted by Fagan et al. [9], it could not be shown sufficiently that there was sufficient analgesic efficacy with an intra-articular bupivacaine plus adrenaline regimen administered 15 min before surgical intervention. Therefore, we suggest that greater than 15 min intervals are required for adequate analgesic efficacy of intra-articular local anesthetics –especially bupivacaine and, in a similar manner, levobupivacaine - and, therefore, we performed levobupivacaine administrations 30 min before surgical incision as per the studies of Reuben et al. [7] and Tuncer et al. [1].

Various analgesia methods, including systemic analgesics, neuroaxial blocks, infiltrative anesthesia with local anesthetics and intra-articular administration of local anesthetics and opioids, are used for arthroscopy-related pain relief [10-14]. Local anesthetics – especially long acting agents such as bupivacaine along with commonly used agents, like levobupivacaine or ropivacaine – are commonly used intra-articularly [1,7-9]. Certain authors have concluded that bupivacaine is more prone to trigger an inflammatory process than ropivacaine. Levobupivacaine has a similar anesthetic / analgesic profile and less cardiac and central nervous system toxicity compared with bupivacaine [15]. In contrast to bupivacaine, there are limited studies investigating chondrotoxicity of levobupavaine. We have previously demonstrated there are no harmful effects from levobupivacaine on rat knee cartilage tissue [16]. We injected 0.25 ml (5 mg/ml) levobupivacaine into the right knee joint of rats and 0.25 ml saline into the left knee joint. We discerned no significant differences between levobupivacaine and the control groups in terms of inflammation in the articular and periarticular tissues and synovium except on the first day which could have been because of the intra-articular injection [16].

There is no consensus on the optimal intra-articular dose of levobupivacaine, however in a study conducted by Jacobson et al. [17], high dosages of intraarticular levobupivacaine (5 mg / ml v.s. 2.5 mg /ml) was found more effective then low dosages of the same agent. As such, we employed intra-articular levobupivacaine at 5 mg/ml dosages in the present study. Additionally, no complications and/or side effects were recorded in any of the patients in this study that received intra-articular levobupivacaine or saline.

Many investigations have compared the efficacy of more than one agent administered through the intra-articular route while here, we studied levobupivacaine solely and compared it to strictly saline in order to determine the isolated preemptive effect of levobupivacaine on postoperative pain. Furthermore, all intra-articular injections were made by same blinded anesthesiologist to prevent possible injection-related confounding factors, such as difference in injection site, angle and experience level.

Conclusion and Recommendations

According to the short literature review presented earlier, we can clearly state that the present study is unique because of the preemptive administration and demonstrable effectiveness of levobupavacaine in knee surgery. In this work, we found that preemptive analgesia with intra-articular 5 mg / ml (20 ml total volume, 100 mg total dose) of levobupivacaine provided sufficient pain relief with a longer time to first analgesic request and decreased opioid consumption compared to normal saline.

Future studies investigating both the clinical outcomes and histopathological consequences on chondrocytes/knee cartilage tissue with preemptive levobupivacaine alone or combined with other agents may gain insight into the effect of intra-articular route of local anesthetics on pain relief after arthroscopic surgical knee interventions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Tuncer B, Babacan CA, Arslan M. The pre-emptive analgesic effect of intra-articular bupivacaine in arthroscopic knee surgery. Acta Anaesthesiol Scand 2005;49:1373-7.
2. Gristwood RW. Cardiacand CNS toxicity of levobupivacaine: strengths of evidence for advantage over bupivacaine. Drug Saf 2002 25:153–63.
3. Tuncer B, Babacan A, Arslan M. Preemptive intraarticular tramadol for pain control after arthro-

scopic knee surgery. Agri 2007;19:42-9.
4. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatmet of postoperative pain.Br J Anaesth 1993;70:434-9.
5. Gatt CJ Jr, Parker RD, Tetzlaff JE, Szabo MZ, Dickerson AB. Preemptive analgesia: its role and efficacy in anterior cruciate ligament reconstruction. Am J Sports Med 1998;26:524-9.
6. Lundin O, Rydgren B, Sward L, Karlsson J. Analgesic effects of intraarticular morphine during and after knee arthroscopy: a comparison of two methods. Arthroscopy 1998;14:192-6.
7. Reuben SS, Sklar J, El-Mansouri M. The preemptive analgesic effect of intraarticular bupivacaine and morphine after ambulatory arthroscopic knee surgery. Anesth Analg 2001;92:923-6.
8. Tetzlaff JE, Dilger JA, Abate J, Parker RD. Preoperative intraarticular morphine and bupivacaine for pain control after outpatient arthroscopic anterior cruciate ligament reconstruction. Reg Anesth Pain Med 1999;24:220-4.
9. Fagan DJ, Martin W, Smith A. A randomized, double-blind trial of pre-emptive local anesthesia in day-case knee arthroscopy. Arthroscopy 2003;19:50-3.
10. Raj N, Sehgal A, Hall JE, Sharma A, Murrin KR, Groves ND. Comparision of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. Eur J Anaesthesiol 2004;21:932-7.
11. Dernedde M, Stadler M, Bardiau F, Boogaerts J. Continuous epidural infusion of large concentration/small volume versus small concentration/large volume of levobupivacaine for postoperative analgesia. Anesth Analg 2003;96:796-801.
12. Jacobson E, Forssblad M, Rosenberg J, Westman L, Weidemhielm L. Can local anesthesia be recommended for routine use in elective knee arthroscopy? A comparison between local, spinal and general anesthesia. Arthroscopy 2000;16:183-90.
13. Kalso E, Smith L, McQuay HJ, Andrew Moore R. No pain, no gain: clinical excellence and scientific rigour-lessons learned from IA morphine. Pain 2002;98:269-75.
14. Rosseland LA, Stubhaug A, Grevbo F, Reikeras O, Breivik H. Effective pain relief from intraarticular saline with or without morphine 2 mg in patients with moderate-to-severe pain after knee arthroscopy: a randomized, double-blind controlled clinical study. Acta Anesth Scand 2003;47:732-8.
15. Ivani G, Borghi B, Van Oven H. Levobupivacaine. Minerva Anestesiol 2001;67:20-3.
16. Erden IA, Altinel S, Saricaoglu F, Zeybek ND, Akinci SB, Asan E, et al. Effect of intra-articular injection of levobupivacaine on articular cartilage and synovium in rats. Anaesthesist 2012;61:420-3.
17. Jacobson E, Assareh H, Cannerfelt R, Anderson RE, Jakobsson JG. The postoperative analgesic effects of intra-articular levobupivacaine in elective day-case arthroscopy of the knee: a prospective, randomized, double-blind clinical study. Knee Surg Sports Traumatol Arthrosc 2006;14:120-4.